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ON ULCERATIVE ENDOCARDITIS.

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WITH A REPORT OF CULTIVATION AND INOCULATION EXPERIMENTS.

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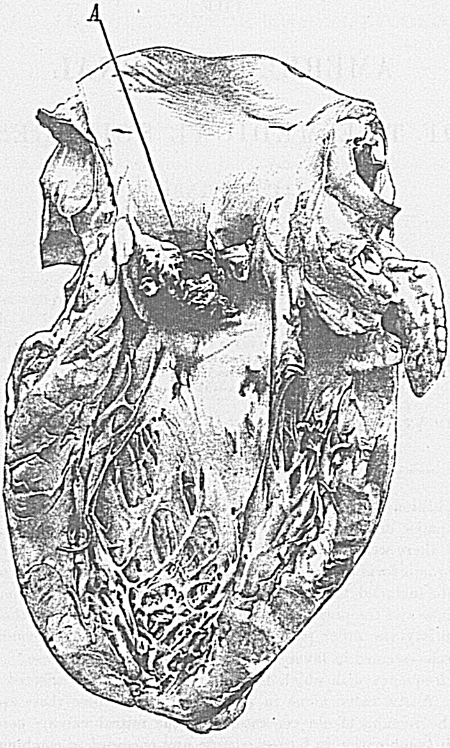
IN addition to the cases of simple endocarditis which were analyzed in my paper on right-sided endocarditis in the April number of this journal, there were 14 cases which seemed to belong to the ulcerative or malignant form of the disease. I am doubtful whether two of these should be included, for although the character of the vegetations, their luxuriance and the presence of micrococci, was suggestive of the malignant variety, the other pathological features—notably the condition of the spleen—seemed in favor of the simple form of the disease.

The frequency with which the different valves were affected was as follows: Aortic valve alone in 7 cases (in one of these there appeared to be the remains of old vegetations on the mitral valve); *aortic* and *mitral* in combination in 6 cases; *aortic* and *tricuspid* in combination in 1 case. The *aortic valve* was, therefore, affected either alone or in combination in 14 cases = 100 per cent.; the *mitral* in 6 cases = 42.85 per cent.; the *tricuspid* in 1 case = 7.14 per cent.

These results appear to be exceptional; for Osler, in his analysis of more than 200 cases, found that "the aortic and mitral valves were affected together in 41 cases; the aortic alone in 53; the mitral alone in 77; the tricuspid in 19; the pulmonary valves in 15; and the heart-wall in 33."[1]

FIG. 1.



Interior of the left ventricle, showing extensive ulcerative endocarditis of the anterior coronary segment in the case of A. Blythe.

The letter A points to a large ragged perforation in the valve segment.

The aortic valve segments were *perforated* or *ulcerated through* in 8, and the mitral in 3 cases. Aneurisms were present on the mitral valve

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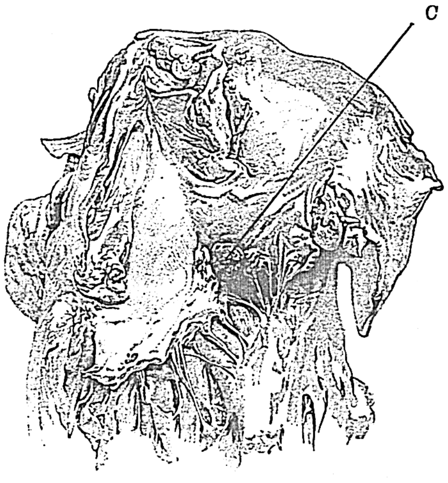
[1] Gulstonian Lectures on Malignant Endocarditis, Lancet, March 7, 1885, p. 417.

in 1 case; on the aortic segments in several of the cases in which the valve segments were perforated; and at the root of the aorta (in or immediately above the sinuses of Valsalva) in 2 cases. In 1 case there was an aneurism of the left ulnar artery, which had ruptured into the tissues of the forearm, and formed a large false sac. *Rupture of the chordæ tendineæ* was met with in 1 case. *Vegetations* were present *on the endocardium* in several instances (though they are only noted in the ledger as having been present in 1 case); there were also vegetations *at the root of the aorta* in 3 cases. In several instances, the vegetations at the root of the aorta, and perforation of the anterior flap of the mitral valve, were clearly due to the friction and impaction of long, pendulous vegetations attached to the aortic segments. *Chronic valvulitis* was certainly present in 7, and probably in at least one or two other cases.

FIG. 2.



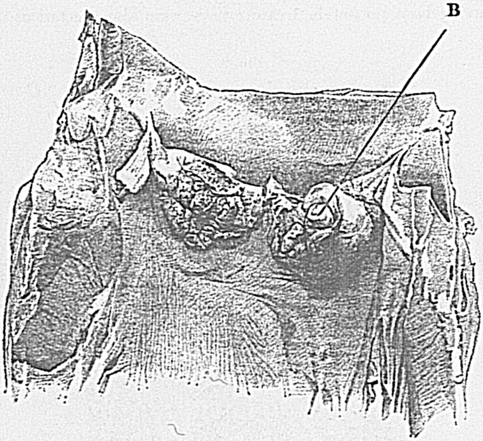
The interior of the right auricle, the tricuspid valve, and part of the interior of the right ventricle, in the case of A. Blythe, showing a small aneurism (C) which sprang from the bottom of the left coronary sinus of Valsalva, and projected into the cavity of the left auricle, at the level of the attachment of the tricuspid valve.

The naked-eye appearances which the lesion presented were very various; some of them are shown in Figs. 1, 2, 3, 4, and 5.

In two cases the vegetations were of a greenish-yellow color, an appearance which Osler has also described.[1]

The size of the heart is not noted in 1 case, in 2 it was normal, and in the remaining 11 cases the organ was enlarged, often to a very considerable degree.

Fig. 3.



The aortic valve in a case of ulcerative endocarditis, showing luxuriant flat vegetations on two of the segments.

The more important associated pathological changes were as follows:

(1) Spleen.—The condition of the spleen was noted in all but one case;[2] the organ was invariably enlarged. In one case its structure appeared normal to the naked eye; in two cases it was dark colored, firm, and congested, resembling the ordinary spleen of old-standing mitral disease; in one case it appeared to be waxy; in all the other instances it was soft, pulpy, and fever-like. In two cases ordinary hemorrhagic infarcts are stated to have been present in the spleen, but the number of cases in which this lesion occurred was probably greater, for I have a strong impression that the presence of infarcts has in more than one case been omitted by the clinical clerk in transcribing the notes.

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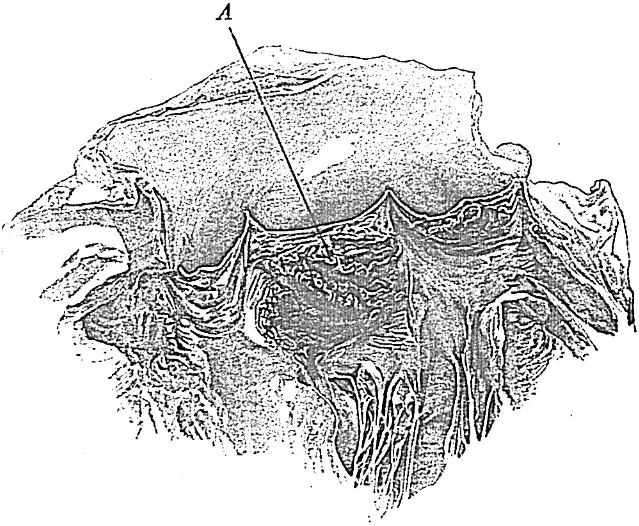
[1] Gulstonian Lectures on Malignant Endocarditis, Medical News, March 21, 1885, p. 310.

[2] In the case in which the spleen was not examined, "permission" was strictly limited to the cavity of the thorax.

In one case the spleen was in a state of commencing suppuration, innumerable small infective emboli being scattered throughout its substance.

(2) Lungs.—Acute croupous pneumonia was certainly present in 3, and probably in 7 of the 14 cases; in 1 instance both lungs were affected with well-marked gray hepatization; in 2 cases there was well-marked red hepatization, in 1 both lungs being affected, and in the other the left only involved; in 4 cases both lungs were affected with œdema and congestion, which seemed to be pneumonic.

Fig. 4.

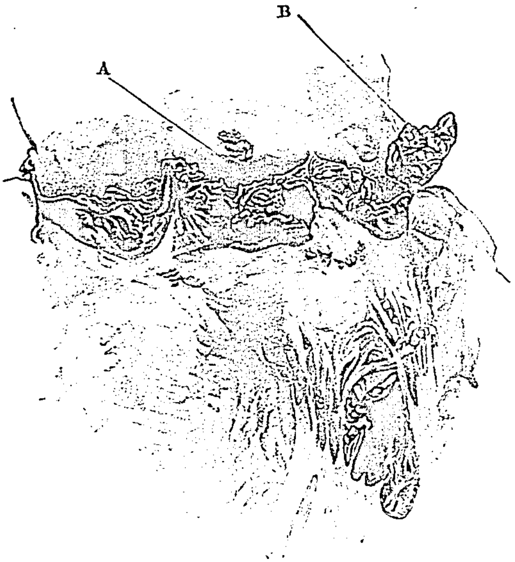


Aortic valve in a case of ulcerative endocarditis, showing heaped-up masses of moderately firm vegetations on the intercoronary and left coronary segments, both of which were perforated in their centres.

In 3 cases œdema and congestion of a simple (non-pneumonic) kind were present; in 1 there was marked brown induration; in 1 marked emphysema; in 1 ordinary hemorrhagic infarcts and patches of pulmonary apoplexy; and in 1 case empyema with compression of the right lung, and recent pleurisy on the opposite side.

(3) KIDNEYS.—In 1 case the condition of the kidney was not ascertained; in 5 cases the weight was normal; in the remaining 8 cases the kidneys were enlarged, in some instances very markedly so. Ordinary hemorrhagic infarcts were present in 3 cases; in 1 instance both kidneys were studded with septic infarcts and miliary abscesses; in 1 case many small ecchymoses, indicative of minute microscopical infarctions, were scattered throughout the cortex. In 2 cases the usual appearances of acute (non-suppurative) nephritis were present.

FIG. 5.



Aortic valve in a case of ulcerative endocarditis, showing extensive ulceration and a large stalactite-looking vegetation (B) projecting from the left coronary cusp. Some small vegetations (A) are present at the base of the aorta, and on the wall of the ventricle, just below the aortic orifice.

(4) NERVE CENTRES.—In 8 cases the condition of the nerve centres was not ascertained. In 2 of the remaining 6 cases, there was well-marked cerebral meningitis; in 1 of these cases the left middle cerebral artery was plugged with a recent infarct; the Island of Reil was in a

state of commencing softening, and there were numerous small punctiform ecchymoses in the gray matter of each hemisphere; in the other case, the membranes of the spinal cord were also in a state of commencing inflammation. In a third case, basilar meningitis was just commencing; in a fourth, the membranes were adherent (the result of old disease) over the left ascending parietal and frontal convolutions.

In 4 of the 6 cases in which the nerve centres were examined there were small hemorrhages in the retinæ.

(5) SKIN AND CUTANEOUS CELLULAR TISSUE.—Punctiform ecchymoses and purpuric spots were noted as having been present in 3 cases, but I feel certain that they were more frequently observed. In 1 case, in which there was no croupous pneumonia, an herpetic eruption was present on the lips. In 6 cases the feet and legs were œdematous, and in 3 of these cases the œdema was great.

(6) LIVER, INTESTINE, UTERUS.—In no case were miliary abscesses or infarcts found in the liver; in several instances the organ presented the ordinary appearances due to chronic venous engorgement; in 1 case there had evidently been previous syphilitic hepatitis; and in 1 case there was hypertrophic cirrhosis.

In 3 instances at least (I think the number was greater) punctiform ecchymoses and small hemorrhages were present on the gastro-intestinal mucous membrane. In one case, the uterus was enlarged, the patient having been prematurely confined shortly before her admission to hospital. A rough, granular-looking mass, the remains apparently of a portion of placenta, projected into the uterine cavity; and there was an extravasation of blood about the size of a bean on the serous surface of the organ; notwithstanding these suggestive appearances, micrococci were not detected in the tissues of the uterus.

(7) THE PRESENCE OF MICROÖRGANISMS IN THE VEGETATIONS AND TISSUES.—In 3 instances the cardiac vegetations were not examined for microörganisms; in all the remaining 11 cases, microörganisms were found. In every instance, the organism was a micrococcus of small size which was either scattered through the substance and on the surface of the vegetation, or collected on the surface in round masses; in no case were encapsuled masses of micrococci observed; in 6 cases, the vegetations were literally teeming with micrococci.

METHOD OF STAINING.—Gram's method was in all instances employed, methyl-violet, prepared according to Ehrlich's method (as recommended by Dr. M. Afanassiew, in the *Edinburgh Medical Journal* for February, 1885), being, as a rule, substituted for gentian-violet.

In the examination of large sections of delicate and fragile tissue, such as the brain and spleen, the following modification of the usual method of carrying out Gram's process was employed, and will, I think, be found an improvement. It enables the section to be manipulated with much greater freedom, and prevents the tearing and breaking of the tissue, which in my hands so frequently occur in the process of transferring a large and delicate section from the " lifter " and spreading it out on the slide preparatory to the final mounting. It also enables one to regulate with greater precision and accuracy, than is, I think, possible by the ordinary Gram's method, the washing out of the coloring matter from the tissues by the absolute alcohol and oil of cloves respectively; finally, it has yielded in my hands more permanent preparations than the ordinary method.

The process is as follows:

The section having been (1) stained with methyl-violet; (2) washed for a second or two in distilled water; (3) immersed for two or three minutes in a solution of iodine in iodide of potassium; and (4) again washed in distilled water, as in the ordinary Gram's method; is (5) placed in a watch-glass containing absolute alcohol until the greater part of the coloring matter is washed out, but the decolorization should not be carried so far as in the ordinary method; (6) the section is then placed for a minute or two in a solution of eosine, from which (7) it is transferred to a basin of distilled water, where it may remain without injury for two or three hours—a great convenience to the operator. (8) The section is then floated on to, and carefully spread out on, a glass slide, as in the ordinary method of mounting large microscopical sections of delicate tissue. (9) It is next treated, while on the slide, with successive doses of absolute alcohol, until it is completely dehydrated and sufficiently decolorized. In the case of very thin sections, which have been already pretty well decolorized, one or two doses of absolute alcohol dropped from a bottle on to the slide, and allowed to flow over the specimen, are usually sufficient. (10) The excess of alcohol is allowed to flow off the section, the slide being inclined to one side to facilitate drainage; the slide round the margins of the section is carefully dried with the finger or a piece of fine cambric; and (11) *while the section is still moist*, a small quantity of oil of cloves is dropped on to the slide at one side of the section; the slide is then inclined to the opposite side and the oil of cloves allowed to flow *under* the section, the preparation being supported in position by the point of a needle placed on the edge opposite to that from which the oil of cloves is flowing; the section may, of course, be *held* in position by the needle being placed through it at the side *from which* the oil of cloves is running, but this I find is more likely to produce tearing in the case of very delicate tissues, such as brain and spinal cord. When the preparation is *thoroughly cleared*—it must be perfectly transparent—the slide is still further inclined, and the oil of cloves carefully wiped away from the edge of the section. (12) One or two large drops of zylol balsam are then placed on the section (the amount of balsam must, of course, be varied with the size of the section) and the cover-glass is placed in position.

A little practice will enable the operator to manipulate the section on the slide with great facility, and to determine the amount of absolute alcohol and oil of cloves which is required. Specimens which are properly prepared in this way retain their color; the micrococci in some of my sections, which were mounted a year ago, are still quite as brightly stained as when the preparations were first made. To insure permanency, each step in the process must be *thoroughly* carried out—the water in the section must be completely removed by the absolute alcohol—the alcohol must be thoroughly removed by the oil of cloves. If the section is not quite transparent after being treated with oil of cloves, it must be again treated with alcohol and again cleared—any excess of oil of cloves must be drained away by inclining the slide—and the amount of zylol balsam placed on the section must be more than is required for the mere mounting of the preparation, in order to drive out any oil of cloves which still remains in the section.

After mounting, the preparation should be placed aside on a flat surface, any balsam which exudes being absorbed by small pieces of blotting paper placed round the margins of the cover-glass. After a day or two a small weight may be placed on the cover-glass; but if this is done, care must be taken that the weight is not so heavy as to squeeze out or destroy the continuity of the sections. Heavier weights may from time to time be substituted; the excess of balsam is in this way gradually removed, and a preparation finally obtained which is quite flat and free from wrinkles, and the whole of which can be examined with high magnifying powers.

The time and labor required for histological investigations of this description are very great, and I have not attempted to make an exhaustive examination of all the peripheral organs in every case. In one case, however, in which the clinical symptoms were of the "pyæmic type," and in which infective emboli were scattered in extraordinary numbers throughout the body, a thorough examination of all the organs was made.

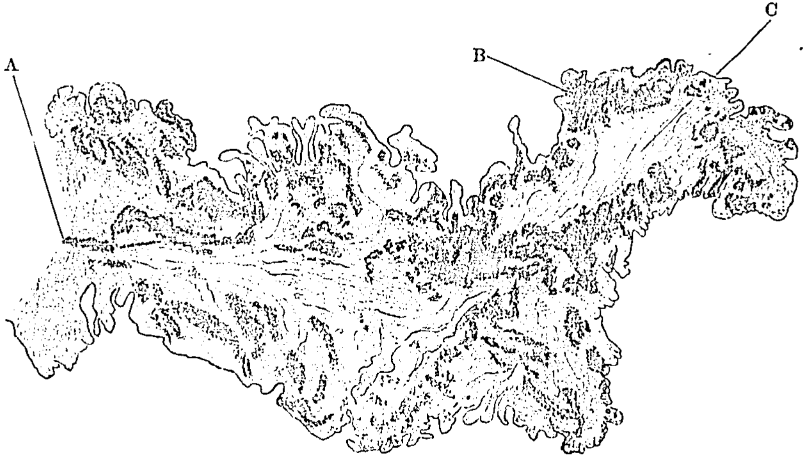
The clinical history of this case was as follows:

CASE. Robert Hardie, æt. thirty-four, was admitted to the Edinburgh Royal Infirmary, under the care of Professor Annandale (to whom I am indebted for the clinical history of the case), on October 18, 1884, suffering from a urethral stricture and perineal abscess.

The abscess was evacuated with proper precautions, on the day of admission, and soon healed without febrile disturbance or other untoward symptoms.

On Nov. 10th, the stricture was divided internally by Maisonneuve's method; the operation was followed by ups and downs in temperature, albuminuria, well-marked cardiac murmurs, and symptoms of cerebral meningitis.

Fig. 6.



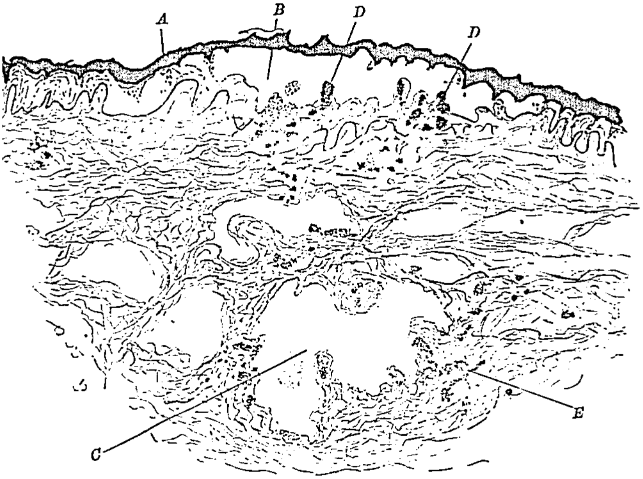
Camera lucida drawing of a section of a cardiac vegetation in ulcerative endocarditis, showing masses of micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 4; ocular 3; tube in; and drawing reduced from 7 to 5½ inches. A, points to the base of the vegetation; C, to its free end; B, to a dense mass of micrococci stained blue with the methyl-violet; the light parts of the vegetation are in the actual preparation stained red by the eosine; the dark portions are large masses of micrococci.

On Nov. 24th, the patient died. The *post-mortem* examination was made forty-eight hours after death, the abdomen being very slightly green at its lower part from commencing decomposition. There were no internal signs of putrefaction. There was no inflammatory lesion in the position of the perineal abscess; and the urethra, except that a band of mucous membrane extended longitudinally along it at the seat of the stricture, appeared to be healthy.

The naked-eye lesions which were found, were as follows:

Heart: Aortic valve, all segments covered with very soft and luxuriant vegetations, the intercoronary segment ulcerated through, cone-diameter 1.05; mitral valve healthy, cone-diameter 1.7; tricuspid valve healthy, cone-diameter 2; pulmonary valve healthy, cone-diameter 1.25; weight of heart $9\frac{1}{2}$ ozs.; left ventricle 4 in. long, wall $\frac{5}{8}$ in.; right ventricle, length $3\frac{1}{2}$, wall $\frac{1}{8}$. *Spleen:* 1 lb. 1 oz.; very soft, of a rusty brown color; in places yellow and apparently in a state of commencing suppuration. *Kidneys* weigh 8 ozs.; numerous small projecting abscesses on the surface surrounded by a ring of softening and congestion; on section many streaks of inflammation extending through the cones to the cortex, and forming large wedge-shaped inflammatory lesions, in the midst of which the small abscess points, previously described, were sit-

FIG. 7.



Camera lucida drawing of a section of the skin in ulcerative endocarditis, showing numerous masses of micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 4; ocular 3; tube out; and drawing reduced from 7 to 5 inches. The section was made through a purpuric patch and small abscess in the subcutaneous cellular tissue. A, free surface of the skin, which always contains organisms, and is consequently deeply stained of a blue color. B, points to the purpuric patch; the cuticle is separated from the cutis (D, D,), which contains large masses of micrococci. C, small abscess in the subcutaneous tissue; numerous masses of micrococci (E) are seen in the wall of the abscess and in the surrounding tissue.

FIG. 8.

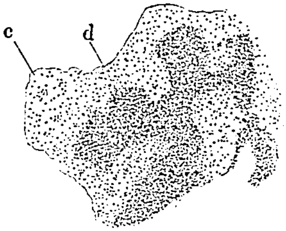


FIG. 9.

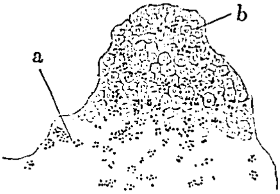


FIG. 8.—Camera lucida drawing of a minute portion of a cardiac vegetation in ulcerative endocarditis, showing enormous numbers of micrococci, in masses (d) and scattered throughout the tissue. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3 tube out.

c, free surface of the vegetation.

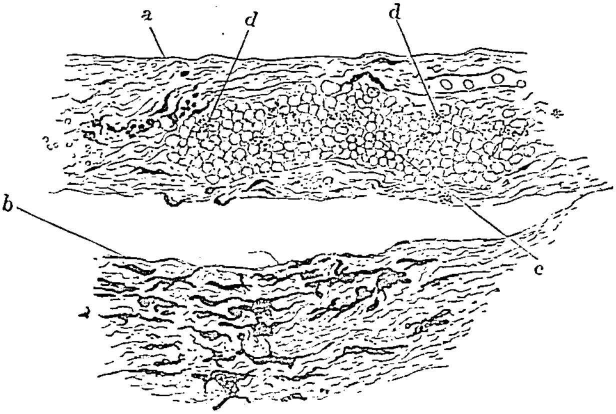
NOTE.—To see the individual micrococci, the drawing should be held about six inches from the eye.

FIG. 9.—Camera lucida drawing of a section of a papilla of the skin in ulcerative endocarditis, showing micrococci in clusters and scattered. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out.

NOTE.—To see the individual micrococci, this drawing should be held about six inches from the eye.

At a the micrococci are only represented; at b the cells of the tissue (pus cells?) have been drawn in.

FIG. 10.



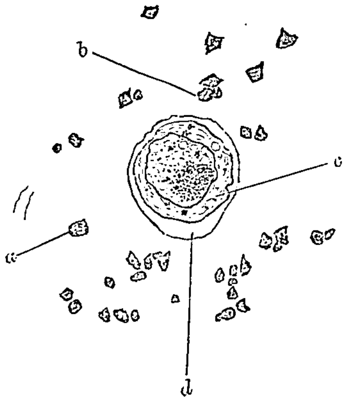
Camera lucida drawing of a section of the choroid coat of the eyeball in ulcerative endocarditis, showing micrococci in the midst of pus cells. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out.

a, free surface of the choroid from which the retina has been detached; b, deeper layer of the choroid, containing stellate pigment cells; c, collection of pus cells, in the midst of which numerous micrococci (d, d) are situated.

NOTE.—To see the individual micrococci, the drawing should be held about six inches from the eye.

uated; weight: right 8 ozs., left 9 ozs. *Lungs:* a few old adhesions at both apices, very congested, œdematous and friable; commencing pneumonia; weight: right 1 lb. 13 ozs., left 1 lb. 10 ozs. *Brain:* here and over the vertex, more especially at the top of the left frontal lobe, also over the base, numerous small punctiform ecchymoses and patches of increased vascularity in the membranes; embolism of middle cerebral artery, commencing softening of the Island of Reil; punctiform hemorrhages here and there in the gray matter of the hemispheres; weight, 3 lbs. 5 ozs. Two or three small hemorrhages in each retina. *Skin:* Purpuric spots on the fingers, small abscess on left forearm. *Liver:* 4 lbs. 3 ozs., fatty. *Urethra,* which had been divided by internal cutting operation for stricture, free from any inflammatory condition; a ridge of mucous membrane seemed to extend along the canal for some distance. Some inflammatory swelling of left testis, but no distinct abscess.

FIG. 11.



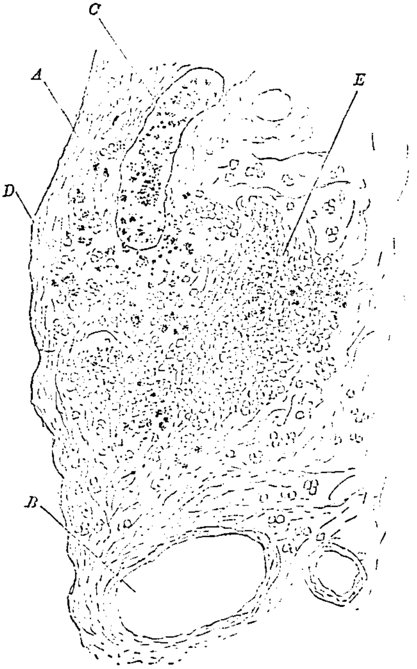
Camera lucida drawing of a section of the superficial layer of the gray matter of the brain in ulcerative endocarditis, showing an artery which contains micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out.

a, *b*, corpuscles of the neuroglia and small nerve cells; *c*, artery, the walls of which are thickened: the vessel is filled with red blood-corpuscles, and contains numerous micrococci which have been drawn rather larger than they are in the actual specimen, in order that they may show in the woodcut; there are also some micrococci in the arterial coats; *d*, lymphatic space surrounding the vessel.

Portions of the cardiac vegetations, spleen and kidneys, were placed in clean glass-stoppered bottles and immediately sent to Mr. Hare, and formed the material with which the first series of his cultivation and inoculation experiments were made. (See Mr. Hare's report, page 44.)

Portions of all the tissues and organs were hardened both in absolute alcohol and in Müller's fluid. On subsequent microscopical examination, micrococci were found in immense numbers in the cardiac vegetations, kidneys, membranes of the brain, cortex of the brain, choroid coat of the eye, skin, and testis. I failed to detect micrococci in the infarction which plugged the left middle cerebral artery, and in the liver.

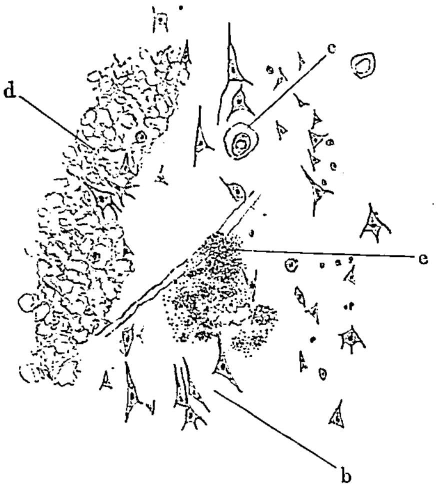
FIG. 12.



Camera lucida drawing of a section through the membranes of the brain in ulcerative endocarditis, showing numerous collections of micrococci in the midst of pus cells and in a vein. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out; drawing afterward reduced from 6 to $4\frac{3}{4}$ inches.

A, free surface of the portion of the membranes dipping down between two convolutions; *B*, large artery at the bottom of the sulcus; *C*, vein containing numerous micrococci; *D*, mass of micrococci; *E*, pus cells, in the midst of which there are numerous micrococci.

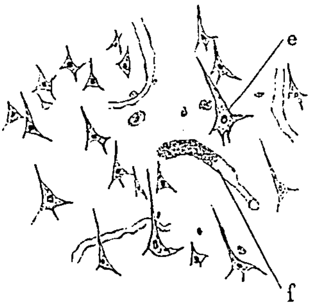
FIG. 13.



Camera lucida drawing of a section of the cortex of the brain in ulcerative endocarditis, showing a patch of cerebritis, and a large mass of micrococci in the adjacent brain-tissue Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 8; ocular 3; tube out.

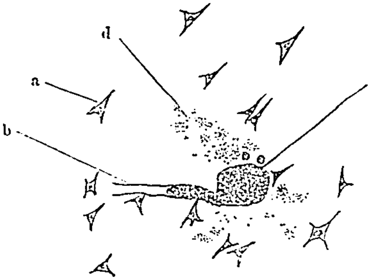
d, The portion of the gray matter affected with acute cerebritis; b, healthy portion of gray matter containing pyramidal nerve cells, the neuroglial basis is not shown in the drawing; c, transversely divided vessel; e, mass of micrococci extravasated around a small vessel.

FIG. 14.



Camera lucida drawing of a section of the gray matter of the brain in ulcerative endocarditis, showing a small vessel (f) plugged with micrococci, and large pyramidal nerve-cells (e). Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out.

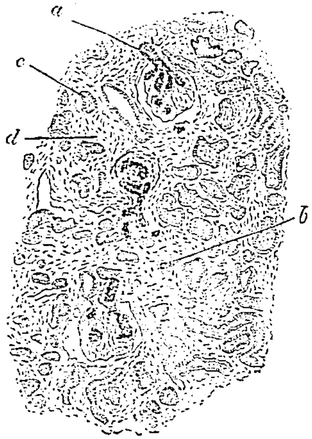
FIG. 15.



Camera lucida drawing of a section of the gray matter of the brain in ulcerative endocarditis, showing a bloodvessel plugged with micrococci, and micrococci in the adjacent brain-substance. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out.

a, Small pyramidal nerve cell; b, capillary vessel plugged with micrococci; c, a larger vessel (from which the capillary springs), also plugged with micrococci; d, micrococci in the brain-substance.

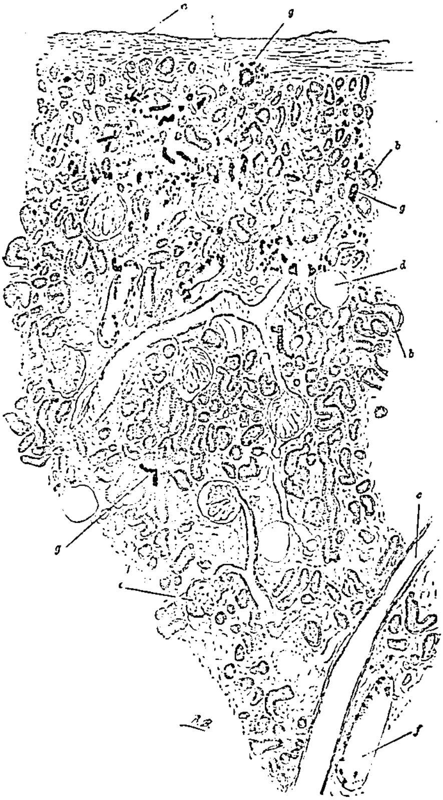
FIG. 16.



Camera lucida drawing of a section of the cortex of the kidney in ulcerative endocarditis, showing three Malpighian tufts, the vessels of which are plugged with micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 4; ocular 3; tube out.

a, Vessel proceeding to the Malpighian tuft at the top of the drawing, stuffed with micrococci; *b*, a mass of micrococci in the intertubular tissue, which is infiltrated with round cells not shown in the drawing; *c*, transversely divided renal tubule; *d*, intertubular tissue.

FIG. 17.



Camera lucida drawing of a section through the cortex of the kidney in ulcerative endocarditis, showing numerous masses of micrococci stained with methyl-violet and eosine; and mounted in zylol balsam. × Hartnack, objective 4; ocular 3; tube out; and drawing reduced from 7½ to 6 inches. Plugs of micrococci, represented as black masses, fill the small vessels, and masses of micrococci are situated in the large veins. The intertubular connective tissue is much increased and infiltrated with round cells, which are not represented in the drawing.

a, free surface of the capsule; *b*, *b*, transversely divided renal tubules; *c*, inflamed Malpighian tuft; *d*, empty Malpighian capsule; *e*, large artery longitudinally divided; *f*, longitudinally divided vein containing micrococci in masses; *g*, *g*, *g*, masses and plugs of micrococci.

The accompanying figures, which are exact photographic reproductions of camera lucida drawings made by myself, show the appearance which sections of the different organs presented, and render any further description than that which is attached to the woodcuts, unnecessary.

Micrococci have been drawn rather larger than the actual size, in order that they might be distinctly seen in the woodcuts. The magnifying power was, as a rule, a No. 9 immersion, Hartnack, eye-piece No. 3, and tube drawn out.

FIG. 18.

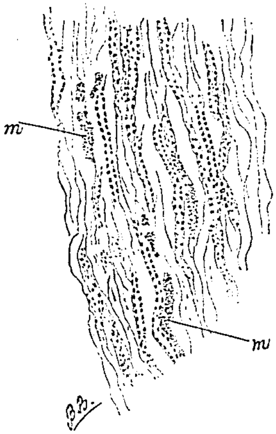


FIG. 19.

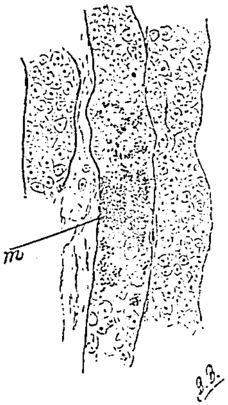


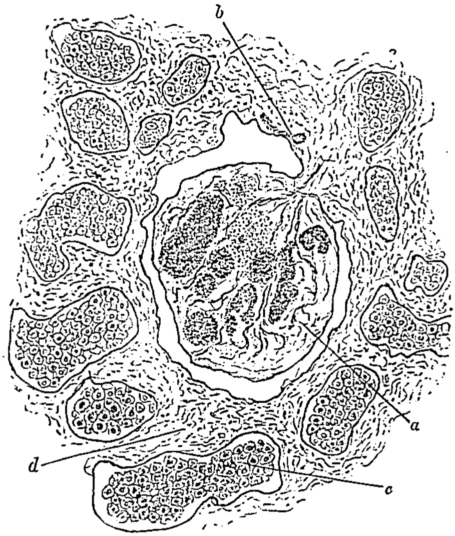
FIG. 18.—Camera lucida drawing of a longitudinal section through the pyramidal portion of the kidney in ulcerative endocarditis, showing masses of micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 4; ocular 3; tube out.

m m, micrococci masses.

FIG. 19.—Camera lucida drawing of a longitudinal section through the pyramidal portion of the kidney in ulcerative endocarditis, showing three renal tubules, the central one containing micrococci (m). Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out.

The frequent association of acute croupous pneumonia with ulcerative endocarditis is of great interest from an etiological point of view, as Osler has so forcibly pointed out in his admirable Gulstonian Lectures. In two of the three cases in this series, in which well-marked acute croupous pneumonia was present, I detected micrococci in the exudation filling the air-cells of the lung, but I failed to satisfy myself that they were identical with the micrococci in the cardiac vegetations. The micrococci in the air-cells appeared to be larger than the micrococci in the vegetations. My observations, however, on this point have not as yet been sufficiently accurate or extensive to enable me to form a satisfactory judgment; and in the mean time I reserve my opinion on the point. Probably this interesting question is more likely to be decided by cultivation and inoculation experiments than by simple microscopical examination. My pathological experience clearly shows that during certain seasons (during certain years or certain months) acute croupous pneumonia and ulcerative endocarditis are apt to prevail, but I have not found that when acute croupous pneumonia is epidemic, if I may be allowed to use the term, that ulcerative endocar-

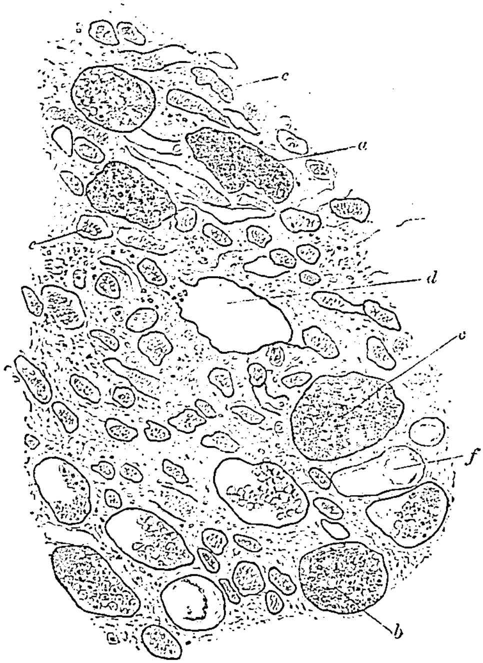
FIG. 20.



Camera lucida drawing of the cortex of the kidney in ulcerative endocarditis, showing a Malpighian tuft stuffed with micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 8; ocular 3; tube out; and drawing reduced from 4 to 3¼ inches. *a*, Malpighian tuft, the vessels of which are plugged with micrococci; *b*, small vessel, passing (?) to the Malpighian tuft, plugged with micrococci; *c*, renal tubule filled with epithelial cells, the outlines of which are more sharply defined in the drawing than in the preparation; *d*, interstitial tissue between the tubules, infiltrated with cells which are omitted from the drawing.

ditis also prevails. My experience in this matter is shown in the Table. I can, however, confidently say that during the past year, when ulcerative endocarditis seemed to be unusually prevalent in Edinburgh, the number

FIG. 21.



Transverse section through the pyramidal portion of the kidney in ulcerative endocarditis, showing transversely divided tubules containing micrococci. Stained with methyl-violet and eosine, and mounted in zylol balsam. × Hartnack, objective 9; ocular 3; tube out; and drawing reduced from 5½ to 4½ inches.

a, "Collecting tube" stuffed with micrococci; *b*, tube containing numerous micrococci in clusters and scattered between the cells; *c*, tube containing scattered micrococci and cells; *d*, empty tube; *e*, bloodvessel; *f*, hyaline cast in a renal tubule.

The epithelium of most of the tubes is proliferating; the intertubular tissue is infiltrated with round cells, the majority of which have, for the sake of clearness, been omitted from the drawing.

NOTE.—For the sake of clearness, the individual micrococci are represented larger than the actual size.

of so-called septic cases which came under my notice was decidedly above the average.

TABLE SHOWING THE MONTHLY DISTRIBUTION OF THE CASES OF ACUTE CROUPOUS PNEUMONIA AND ULCERATIVE ENDOCARDITIS, WHICH WERE EXAMINED POST-MORTEM IN THE EDINBURGH ROYAL INFIRMARY DURING THE YEARS 1882–83, 1883–84, AND 1884–85.

Month.	1882–83.		1883–84.		1884–85.	
	Pneumonia.	Ulcerative endocarditis.	Pneumonia.	Ulcerative endocarditis.	Pneumonia.	Ulcerative endocarditis.
November,	2	1	2	0	0	2
December,	4	0	1	1	2	0
January,	3	0	1	0	2	0
February,	5	0	2	0	0	1
March,	4	1	2	0	2	0
April,	4	0	4	0	0	0
May,	4	0	1	0	1	3
June,	3	0	3	0	0	0
July,	2	0	1	1	5	0
August,	0	0	1	1	0	0
September,	2	0	0	0	0	0
October,	0	1	2	0	4	2
Total,	33	3	20	3	16	8

The detection of micrococci in the inflamed cerebral meninges, and in the vessels and substance of the cerebral cortex, and the presence of disseminated patches of cerebritis and acute cerebral softening, are very interesting; and afford a satisfactory explanation of the nervous symptoms which are so prominent in some cases of the disease.

The following is the brief record of a very striking and interesting case, in which the symptoms were of the type which Osler has termed "*cerebral.*" I am indebted for the clinical record of this case to my friend, Dr. Berry Hart:

CASE. *Endocarditis of the Cerebral Type*—A. B., aged thirty-one, was seen by Professor Simpson and Dr. Berry Hart for three days only before his death. A week previously Professor Simpson happened to meet the patient by chance, and seeing that he looked ill, advised him to go to bed. Instead of taking Professor Simpson's advice, he went to the country, and only returned to town because no improvement took place. His friends stated, that for some weeks previously he had been greatly out of sorts, complaining of feebleness, suffering from shivering and loss of memory, and that, on one occasion, he had fainted.

He was first seen by Professor Simpson and Dr. Berry Hart on the evening of November[1] 8, 1884. The temperature was then 103.4° F.;

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[1] It is interesting to note that during the month of November, 1884, two fatal cases of ulcerative endocarditis occurred in the Edinburgh Royal Infirmary.

but with the exception of a well-marked presystolic mitral murmur, there were no physical signs of localized disease.

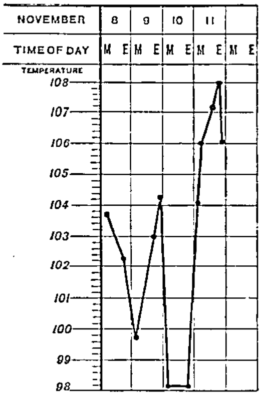
On the morning of the 9th the temperature was 99.8°, and he was troubled with a short cough. Examination of the chest failed to reveal any other physical signs than the presystolic murmur previously described.

On November 10th he seemed better, and the temperature, both morning and evening, was normal.

At 4 A.M. on the 11th, and again at 8.30 A.M., he was seized with a rigor, the temperature rising to 104° F.

At 12.45 P.M., violent delirium set in, with tetanic spasms (opisthotonus), and localized convulsive movements of both arms and of the muscles of expression. The temperature rose to 108° F., and death took place at 5.30 P.M.

FIG. 22.



Temperature chart in the case of A. B., ulcerative endocarditis of the cerebral type.

Post-mortem Examination. Through the kindness of Dr. Berry Hart, I was able to make a post-mortem examination on November 13th. The body was well nourished and muscular. The *mitral valve* presented a well-marked, funnel-shaped contraction admitting with difficulty the forefinger. The auricular surface of the valve was eroded, the margins of the ulcer being covered with a thin layer of recent vegetations; the wall of the left auricle was hypertrophied, but the cavity was in no way dilated; the heart was in other respects normal.[1]

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[1] This case was a remarkable example of "latent" mitral stenosis in which compensation was unusually perfect. It was known that the patient had had a cardiac murmur in childhood; but he subsequently manifested no symptoms of the heart disease; he presented all the appearances of good health: was active, muscular, and had been a good "oar." Shortness of breath, cyanosis, dropsy, and other symptoms which are apt to occur in advanced mitral cases, were completely absent.

The *spleen* was soft and pulpy and greatly enlarged; its exact weight was not ascertained, but it must have been more than one pound. The *membranes of the brain* presented here and there evidences of commencing meningitis, the other organs were normal.

Microscopical Examination. The nerve cells of the cerebral cortex were found to be markedly fatty, but no appearances of cerebritis (such as were present in the case of Robert Hardie, previously described) were found; there was well-marked commencing meningitis; micrococci were detected in the inflamed membranes, but not in the vessels or substance of the cortex. (Whether the fatty degeneration of the nerve cells of the brain was of recent origin; whether it was due to defective blood supply the result of the acute cardiac lesion which had evidently been slowly progressing for some weeks previous to the onset of meningitis; and whether this fatty degeneration of the nerve cells was the only cause of the loss of memory, which was most marked, it is, of course, impossible to say. B. B.)

Remarks by Dr. Berry Hart. This case was exceedingly puzzling, and with the single physical sign of a presystolic murmur, the anomalous crisis on November 10th, as well as the absence of all evidences of emboli, it was exceedingly difficult to come to any definite conclusion. The patient seemed so well on November 10th that we felt that our previously expressed opinion of ulcerative endocarditis was almost unwarranted. We did not attach sufficient importance to the enlargement of the spleen. It is possible that a microscopical examination of the blood might have been helpful. The treatment adopted consisted of the administration of antipyretics, and, at the last, of the free application of iced cloths to the surface of the body.

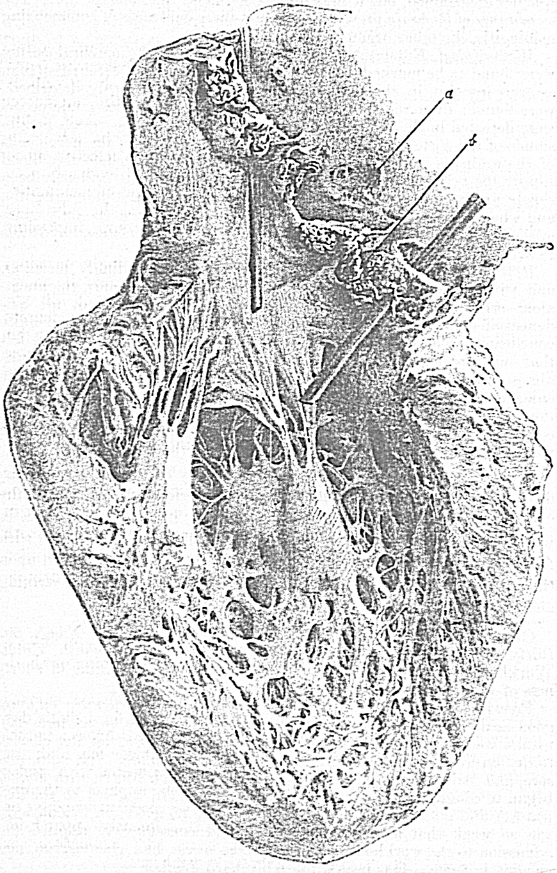
While I am referring to the clinical history of ulcerative endocarditis, it may not be out of place to record briefly three cases of the "cardiac type," under which term I include not only those cases in which patients the subject of chronic valve disease are attacked with febrile symptoms and evidences of a recent endocarditis engrafted upon the old process, but all cases in which the cardiac symptoms are striking and prominent.

CASE. *Ulcerative Endocarditis of Cardiac Type.*—James Naggs, æt. thirty-nine, a street porter, was admitted to the Tynemouth Union Workhouse, under my care, on October 15, 1873, complaining of shortness of breath, cough, and great debility.

Previous History. The patient stated that he had always enjoyed good health, never having been in bed through sickness for a single day until a week ago, when he got wet through, and allowed his wet clothes to dry on him. The next day he was "all of a tremble," felt cold, was sore, and pained all over his body, as if he had been beaten with sticks, began to cough, and had a stitch in the side. He applied to the dispensary and got some medicine which did him no good; in two days he was so weak that he could not stand, and consequently applied for admission to the workhouse hospital. Has never had rheumatism, nor rheumatic fever. Has been a tolerably hard drinker.

State on Admission. Is so weak that he can neither walk nor stand; has a frequent, short, dry cough; complains of pain in the left knee, which is swollen; has had some sweating; is extremely short of breath,

FIG. 23.



Aortic valve in the case of ulcerative endocarditis (James Naggs) detailed in the text.

The aortic cusps are thickly coated with vegetations; two of the segments are ulcerated through, pieces of whalebone being placed in the apertures. The letter *a* points to a small depression (a commencing aneurism) surrounded by minute vegetations at the base of the aorta, and has evidently been produced by the vegetation *b*, which at every systole would be forcibly washed against the aortic wall at this spot.

and very pale, the conjunctivæ and lips being almost bloodless; the feet and legs are œdematous.

Physical Examination. There is marked, visible, jerking pulsation in the carotids; the visible impulse of the heart is larger than normal; the apex is situated in the fifth interspace; a double bellows murmur, the systolic portion being most distinct, is audible at the base of the heart. The temperature is 101.3° F. There are no signs of pulmonary disease or other complications.

Progress of the Case. Under rest, nutritious diet, alcoholic stimulants freely administered, digitalis, and quinine, there was considerable improvement; the temperature became normal; the rheumatic swelling of the knees and the œdema of the feet and legs disappeared; and the patient was able to sit up for the greater part of the day. Toward the middle of November the shortness of breath and debility, which from the first had been such prominent symptoms, increased, and necessitated his lying in bed; the pallor was now more marked even than on his admission.

The heart was now distinctly enlarged, the apex beat being placed in the sixth interspace, and the area of cardiac dulness increased. The double aortic murmur, though still audible, was much less loud; the radial pulse was 104, very weak, at times almost imperceptible. The skin was cool, the rectal temperature was 101.5° F.; sweating at night was a troublesome symptom.

November 29. The patient had a very bad night, the shortness of breath being very great; fine crepitations are to-day audible over both lungs; the radial pulse is 98; temperature normal.

He died suddenly, apparently from syncope, at 6 P. M.

Post-mortem Examination. *30th.* Body very thin; an excess of fluid in the pericardium and in each pleura; no subcutaneous dropsy; both legs œdematous; very marked disease of the aortic valve (see Fig. 23); the heart moderately enlarged, the left ventricle being dilated and hypertrophied; the liver slightly cirrhotic and markedly nutmeg, kidneys healthy; spleen large and congested.

CASE. *Ulcerative Endocarditis of Cardiac Type.*—A. B., aged twenty-one, was seen by me in consultation with my friend, Dr. Croom, on January 17, 1885, suffering from rheumatic fever and endocarditis.

She had consulted Dr. Croom for anæmia a fortnight previously; and two days after her visit had been seized with rheumatic fever. The attack was a severe one, and a mitral systolic murmur and great shortness of breath developed at an early stage of the case.

Under salicylate of soda the joint affection rapidly subsided, and at the time of my visit had almost entirely gone; the temperature, however, still kept up, being 102.2° F.; the breathing was very short and frequent, and fine crepitant and sibilant râles were audible all over the chest; the heart, more especially the right side, seemed considerably enlarged, and a systolic murmur, which was loudest at the left apex, was conducted back to the spine; a faint tricuspid systolic murmur was also audible; there was no pericardial friction.

Under quinine, alcoholic stimulants, ipecacuanha, and digitalis, there was some slight, but only temporary improvement. The difficulty of breathing became more marked; the area of cardiac dulness—apparently the result of acute dilatation, and not of pericardial effusion—became greater.

On January 28th she had a rigor. On the 29th she became hysterical, laughing and crying alternately, and being eccentric, both in her manner and talk, it was obvious that some cerebral complication was developing. There was well-marked inflammation of the right parotid gland.

On the 30th symptoms of cerebral meningitis were distinct, and death took place.

There was no *post-mortem* examination.

Remarks. The rapid development of very free mitral regurgitation; the marked pulmonary engorgement; the rigors; and the occurrence of cerebral meningitis and of parotitis, leave little doubt that in this case the endocarditis was of the ulcerative type. The occurrence of ulcerative endocarditis in the course of ordinary rheumatic fever, and where the heart was previously healthy, is, according to Osler, rare; it is well, however, to remember that it does occasionally occur, and in any case of acute rheumatism in which very free mitral regurgitation, or still more when very free aortic regurgitation is quickly established, the heart having been previously healthy, the presence of the ulcerative forms of endocarditis should, I think, be strongly suspected.

CASE. *Ulcerative Endocarditis of Cardiac Type.*—Robert Reid, æt. ten, was admitted to the Edinburgh Royal Infirmary under the care of Dr. Miller (to whom I am indebted for the clinical record of the case) on April 13, 1885, suffering from a swelling of the left forearm.

Previous History. The swelling was first noticed about a fortnight ago; it arose spontaneously without any injury or other obvious cause; for some time before admission the patient had not looked or felt well; immediately in front of the door of the cottage in which he lived, there is said to be an untrapped drain.

History after Admission. The patient was markedly pale and anæmic; the evening temperature on April 13th was 101.5° F.

15th. Dr. Miller made a longitudinal incision over the swelling and removed a large blood-clot, which weighed about 8 ounces; a bleeding opening was found in what appeared to be the ulnar artery; the vessel was ligatured above and below, and the wound dressed antiseptically.

On the evening of April 15th, the temperature was 100.8° F., and on that of the 16th 102° F.; five grains of quinine were prescribed.

The morning temperature continued to be about normal and the evening temperature varied from 101° to 102° F., until April 26th, when it reached 103° F. The wound was progressing most favorably.

22d. Dr. Wylie examined the patient, and found a mitral systolic and an aortic diastolic murmur; he diagnosed the case as one of ulcerative endocarditis.

The wound continued after this date to heal satisfactorily, but the anæmia, shortness of breath, and extreme debility gradually increased; the temperature continued to fall in the morning and to rise at night; on the evening of May 3d it reached 104° F.

May 21. Dr. Miller very kindly afforded Mr. Hare and myself an opportunity of seeing the patient and of examining the blood. The patient at the time of our visit was extremely short of breath; exceedingly pale, and drowsy from cerebral anæmia. The arterial system was very imperfectly filled with blood, pulsation in the carotids was very visible, jerking and collapsing; there was some swelling of the feet. The heart was considerably enlarged; a soft systolic murmur was present in the mitral area, and a very faint and short diastolic murmur could just be heard at the base of the heart. The area of splenic dulness appeared to be increased; there seemed to be no other complications.

The result of the examination of the blood is detailed in Mr. Hare's report. (See page 48.)

22d. The patient died at 3.15 A.M.

The post-mortem examination was made nine hours after death. Small old adhesions at apex; aortic valve highly incompetent, covered with vegetations; intercoronary segment ulcerated through, vegetations soft and luxuriant, cone diameter 7; mitral valve, small vegetation in each segment, cone diameter 1.2; tricuspid valve healthy, cone diameter 0.95; pulmonary valves normal; weight of heart 11½ ounces; ventricles dilated and hypertrophied. Spleen firm. Malpighian bodies very prominent; color dark purple; one small yellow infarct; kidneys normal to naked eye. Lungs: straw-colored fluid in pleura; some adhesions between lobes; on section, very rose colored, œdematous, and congested at base; on the posterior surface of the lower lobe an area, one inch in diameter, showing small yellow nodules in interlobular septa. Brain normal, excepting some excess of subarachnoid fluid; some micrococci in cardiac vegetations (Mr. Hare's report); none detected in spleen, or in clots, after hardening, contained in aneurism of the radial artery which had been ligatured.

CULTIVATION AND INOCULATION EXPERIMENTS.

Being firmly of opinion that the etiology of ulcerative endocarditis and the relationship of the disease to other infective conditions are more likely to be determined by experimental means than by any other method—an opinion which Professor Osler has since expressed in his Gulstonian Lectures—I requested my friend Mr. Hare to have the kindness to undertake this part of the investigation. Mr. Hare responded to my request with alacrity, and has devoted a large amount of time and labor to the matter. Although the results which he has obtained are as yet, for the most part, negative, they are undoubtedly of great value and interest.

It may not be out of place to quote Osler's summary of the results of previous experiments. "In the way of experimental investigation of the properties of the micrococci," he says, "not much has been done of a satisfactory nature. Heiberg placed bits of vegetations from a puerperal case beneath the skin and in the peritoneal cavity of a rabbit, without effect. Eberth, Birch, and Hirschfeld have produced panophthalmos in the rabbit by inoculating the cornea; and I was able to produce well-marked mycotic keratitis in the same animals with fresh material from the valves in two cases. H. Young, of Manchester, inoculated rabbits with pus from an abscess in ulcerative endocarditis, and was able to detect micrococci in the blood.

"No conclusive culture experiments have yet been made. Grancher has cultivated a microbe from the blood, taken during life with all necessary precautions, but apparently not in series, and no inoculations of animals were made. Cornil has made cultures in gelatine, but apparently no special results have been obtained."

Mr. Hare informs me that the yellow micrococcus which he obtained in his first series of experiments resembles very closely, or is identical with the micrococcus of osteomyelitis. This is a point of great interest, for "in acute necrosis of bone or acute osteomyelitis," Osler says,[1] "a secondary endocarditis may develop, and in some instances the clinical features may strongly resemble malignant endocarditis."[2]

In conclusion, I must take this opportunity of thanking Mr. Hare, not only for undertaking the investigation, but for the opportunities he afforded me of watching the whole inquiry. My thanks are also due to Prof. Chiene for allowing the investigation to be conducted in his laboratory, and for the great interest which he has taken in the research, and to Professor Greenfield and Dr. Woodhead for the facilities which they afforded for carrying on the work.

REPORT.

The following experiments and observations, made with morbid material from certain of the above cases, were carried out by Mr. A. W. Hare, Assistant to Professor of Surgery, at the Bacteriological Laboratory of the Surgical Department in the University of Edinburgh, through the courtesy of Prof. Chiene.

First Series (November, 1884).

These observations were made with material from a case of ulcerative endocarditis (case of Robert Hardie), in which there was a widespread distribution of miliary abscesses in the liver, spleen, and other solid viscera. At the post-mortem examination, portions of these organs were transferred to clean glass bottles, and at once sent to the University for examination.

MICROSCOPICAL APPEARANCES.—The contents of the miliary abscesses were first examined microscopically. The pus was spread in thin films upon cover-glasses, and fixed by Baumgarten's method. The pus was then stained by Gram's double stain (gentian-violet and eosine). Under a power of 700 diameters (Zeiss $\frac{1}{12}$ inch homog. immers.) it was observed that the contents of the abscesses consisted of pus cells and granular débris, together with considerable quantities of a small-sized spherical micrococcus. These organisms appear chiefly as rounded clusters with from 6 to 20 cocci in each ;[1] a few tetrads are also present, and some diplococci, whilst at intervals in the specimens examined monococci are seen. In whichever of these arrangements the organism is observed, the individual unit is uniform in its size, and is of very minute dimensions, measuring very little more than 1 μ in diameter. It takes on any of the aniline dyes, whether acid or alkaline, very easily, and is beautifully demonstrated by Gram's stain.

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[1] Loc. cit., p. 507.

[2] Loc. cit., p. 459.

CULTIVATIONS IN ARTIFICIAL MEDIA.—These were undertaken in the hope of obtaining a pure cultivation of the micrococcus found in the miliary abscesses, with a view to testing further the characters of that organism. For this purpose sterile tubes of Koch's peptonized jelly, and sterile potatoes in glass bell-jars were employed as nutrient soil. A portion of the fresh kidney was divided by a sterile (superheated) knife, in a still atmosphere, the table and the operator's hands being purified with corrosive sublimate solution (one per cent.). Several of the abscesses were thus opened, and a small particle of pus was abstracted from the centre of each on the tips of a series of sterilized platinum wires. With the seed material thus separated, a series of tubes of jelly and of sterile potatoes were inoculated.

RESULT IN JELLY.—One tube reacted, three did not. The tube which reacted showed the following appearances. A gray, finely granular prolongation was seen running down in the gelatine in the line of inoculation. On the seventh day liquefaction set in, and gradually a funnel-shaped liquefied part formed in the centre of the gelatine. At the tenth day the whole circumference of the top of the gelatine was involved in this process, and liquefaction in four weeks had extended to the bottom of the tube, where a fine, amorphous, yellow-gray precipitate was deposited. This yellow-gray deposit was examined microscopically, and found to consist mainly of micrococci of small size; many of these were bereft of life, as was evidenced by the faint staining reaction resulting on the addition of methyl-violet, and large quantities of amorphous débris, amongst which a number of short, straight bacilli were seen.

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[1] This prevailing arrangement of the cocci in clusters of spherical shape is also noticed in pus from osteomyelitic and periostitic cases. It is not due to mechanical conditions as is the rounded shape of micrococcus emboli in the circulating blood, for there is no active movement in the contents of an abscess. It must, therefore, be looked upon as a vital peculiarity of these species of micrococci, to which the name of *sphærococci* might well be applied to differentiate them from other morphological types. The proximate cause of this special feature is to be looked for in the mode of multiplication which is found to occur in the organisms. All micrococci multiply by fission; the cleavage which occurs is either constantly in one plane, producing diplococci or streptococci (chains), alternately in two planes at right angles with one another (tetracocci, sarcinæ), consecutively in each of three planes at an angle of one hundred and twenty degrees with each other, which produces the sphærococcus now noticed, or in an indefinite series of planes in which no regular sequence can be traced, giving rise to the type of staphylococcus. This law also holds true, to some extent, of the forms of growth displayed by the same organisms in artificial media, and gives a possible future basis on which a morphological classification of micrococci may be constructed.

Secondary and tertiary cultivations followed the same course, as did also cultivations in gelatine from the growth which had occurred on the inoculated potatoes. (These cultures were used in Experiments 1 and 2.)

RESULT OF INOCULATION OF POTATOES.—On potatoes the organism grew as a yellow-gray, thick, and moist pellicle. In some parts it was more purely yellow, in others a duller drab color. A pure cultivation of the drab variety of organism was procured and used for the inoculation subsequently described. Two attempts to get pure cultivation of the yellow element failed, and it was not used for inoculation experiments till a subsequent date, when, after repeated failures, a pure growth of the yellow organism was obtained.

The gray colored growth was found to consist of short, straight bacilli in immense clusters. (Used in Experiments 3 and 4.) The yellow growth, when first obtained, consisted solely of micrococci of small size, in irregular clusters. This cultivation was employed subsequently in making inoculation experiments; but at the time it was used it had become contaminated and was not pure, having assumed a buff color and lost its bright yellow tint. (Used in Experiment 5.)

INOCULATION EXPERIMENTS.—These were performed in the Pathological Department of the University, through the courtesy of Professor Greenfield and Dr. Woodhead.

A. With cultures in nutrient jelly.

EXPERIMENT 1.—A tube of jelly in which liquefaction was well advanced, and in which there was a yellow amorphous deposit, was employed in this experiment. The liquefied portion and the deposit were thoroughly mixed by agitating the contents of the tube—and fifteen minims of the turbid fluid thus obtained were slowly injected into the largest efferent vein of the left ear of a rabbit. (Plain white.)

CONTROL EXPERIMENT 1 *a*.—A tube of sterile jelly had its contents liquefied by heat, and fifteen minims of its contents were injected into a vein of the ear of another rabbit. (Black back.)

EXPERIMENT 2.—A small pocket was made in the subcutaneous tissue of a rabbit's ear (black and white "spot") and a drop of turbid fluid from the same cultivation introduced.

RESULT.—In no case was there any reaction, local or general. The animals remained in good health, and after some weeks one of them (black back) was used for another experiment (see Experiment 5). The other two were not made use of again in this series of experiments.

DEDUCTIONS FROM RESULT.—Experiment 1 was intended to ascertain if organisms derived from a case of ulcerative endocarditis were capable of giving rise to the disease when they were introduced into the bloodstream of a lower animal.

Experiment 1*a* was intended as a check upon this by ascertaining whether the constituents of the nutrient media themselves were free from pathogenic properties.

Experiment 2 was devised to obviate the misleading result that might appear in consequence of the immediate devitalization by the blood-stream of foreign elements introduced into it,[1] as is found to be the case with pure cultivations of *bacterium termo;* where the organism is destroyed before it can commence any pathogenetic action. A local focus was therefore established apart from the blood stream, where there was a possibility of the elaboration of products, by absorption of which a secondary infection (autoinoculation, Verneuil) might occur. This was based on the frequency with which ulcerative endocarditis is seen to follow surgical affections in the human subject, the general disease being in these cases secondary to a localized lesion. (This principle was still further developed in Experiment 4.) The negative nature of the results obtained pointed to a series of alternative conclusions, viz.:

1. The organism injected is not a *materies morbi.*

2. The organism cultivated, primarily infective, has become inert:

a. From extraneous contamination (presence of bacillus in tubes along with micrococcus);

b. From intrinsic alteration due to artificial surroundings.

3. The condition of the animal was not such as to admit of the organism exerting its pathogenetic activity, from the animal possessing:

a. Constitutional immunity;

b. Vital activity sufficient to throw off the irritant in these particular cases.

With a view to pressing the matter to a further conclusion, the following experiments were planned and carried out.

B. With cultivations on potatoes.

EXPERIMENT 3.—The gray pellicle cultivated on potato was mixed with liquefied sterile jelly, and an emulsion made, and ten minims of the emulsion were injected into the veins of a (gray) rabbit's ear.

EXPERIMENT 4.—Fifteen minims of the same emulsion were injected into the right auricular vein of another rabbit (brown and white). A sterile needle was introduced into the hind leg of this rabbit, and the periosteum of the tibia detached on the anterior surface for one-third the length of that bone.

RESULTS.—The rabbit used in the latter experiment remained in perfectly good health.

The rabbit used in Experiment 3 developed morbid symptoms in twenty-four hours. It had no appetite, was lazy in its movements, and its eyes were dull and bleared. On the second and third days it grew worse, and on the fourth day seemed moribund; it lay on its side, it was not able to move, and its breathing was labored. On the fifth day it seemed to have passed some crisis and was less affected; and on the sixth day it was much better and recommenced to eat, but did so sparingly.

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[1] Cf. Hiller's experiments with septic organisms. "Die Lehre von der Fäulniss," Berlin, 1879.

On that day it was killed by dividing the spinal marrow high up, and the state of the organs examined. All the organs were found to be healthy, except the lungs, which showed patches of superficial hemorrhage; kidneys normal; spleen small and shrunken. In the heart, some small pink clots were adherent to the tricuspid valve, resembling vegetations, but containing no micrococci. Blood examined, but no microorganisms were detected.

Deductions from Results.—These two experiments were performed to test the pathogenetic activity of the potato cultures; in the latter, a local focus for the action of the organism was provided by the injury to the periosteum, following the plan devised by Becker in his experiments upon infectious osteomyelitis (*Deutsche med. Wochenschr.*, Bd. 9, 1883). The general conclusions are identical with those derived from Experiments 1 and 2.

The rabbit used in Experiment 3 probably suffered from a temporary attack akin to septicæmia, which it threw off on the fifth day. The shrunken spleen points to this conclusion.

These inoculations having been made with the gray film cultivated upon potato, and that film having been subsequently found to consist of bacilli; the yellow film, which had been in the mean time procured pure and found to consist of micrococci, was used as follows:

Experiment 5.—A portion of the cultivation made from the yellow colored part of previous cultivations, which had recently assumed a grayash color owing to the presence of a contaminating bacillus, was scraped off with a sterile knife, mixed with boiled distilled water, and fifteen minims of this emulsion inoculated into the vein of a rabbit's ear (black-backed white rabbit).

Result.—No reaction; animal remained perfectly well.

Conclusions.—The results of this series of experiments are entirely negative. The causes of which these results are the outcome have been already referred to (deductions from Experiments 1 and 2). The two chief features of doubt left are, as to whether these experiments were performed with the supposed *special organism*, and upon a species of animal *susceptible to the disease*. One practical result accrued, however: the decision was come to that in future cases, should they occur, it would be the experimenter's duty to take the organism direct from the local lesion, and introduce it into the circulation or tissues of several species of the lower animals, till one be found liable to an attack of the disease. The difficulties which stand in the way, in this respect, are more of a legal than of an experimental nature.

Second Series (May, 1885).

In this series of experiments, morbid material was made use of from two sources (cases of R. Reid and J. Sweeney). In the former of these cases, the disease was diagnosed during the lifetime of the patient, and the following observations were made by the kind permission of Dr. A. G. Miller.

Microscopical Examination of Blood.—Cover-glasses were prepared, on each of which was a thin film of the patient's blood, which was stained by Gram's method. Out of six specimens examined under the microscope (× 700), two were found to contain microörganisms in very small numbers. Several fields of the microscope had to be carefully searched before a single specimen of the organism could be detected. The organisms demonstrated were all micrococci, in one or two cases in the dumbbell-form (diplococci), but most of those seen were isolated units. They were, as a rule, free in the liquor sanguinis; one leucocyte was found which had ingested a diplococcus. The individual cocci were of small size, measuring barely one μ in diameter.

Cultivation Experiments.—It was impossible to take blood in sufficient quantity from the patient to make direct inoculation with it into animals a promising proceeding. It was accordingly decided to attempt to establish artificial cultivations, by inoculating artificial nutrient media with small doses of the patient's blood. The patient's finger was pricked with a sterile needle, after a thorough preliminary cleansing of the part with soap and water, corrosive sublimate solution (1 : 1000), and absolute alcohol, applied in that sequence. From the centre of the drop of blood which exuded, a trace was removed on the tips of a series of sterilized platinum wires, by which the following media were inoculated: Koch's jelly, agar-agar solution, inspissated serum (hydrocele fluid solidified), and sterile potatoes. The three last-named media were incubated for eight days at blood heat for four hours each day. No reaction occurred in any of these media: they remained perfectly sterile.

Inoculation Experiments.—The autopsy of the case just described was held eight hours after death. A sterile Pravaz syringe was filled with fluid blood from the innominate vein, before that vein was in any other way interfered with. A portion of the vegetation found on the cardiac valve was transferred, with aseptic precautions, to a sterile flask; and these materials were taken to the University for experimental purposes. On the same day another case (J. Sweeny) of ulcerative endocarditis was examined in the post-mortem theatre; a portion of the vegetation on the aortic valves in this case was also removed and employed along with the previously mentioned material in the experiments of this series as follows:

Experiment 1.—Needle of syringe introduced into a large vein of rabbit's ear; and 12 minims of the blood injected slowly into circulation; a single drop of blood was introduced similarly into the subcutaneous tissue of the neck of the same animal (large white rabbit).

Experiment 2.—Large vein of black rabbit's ear laid bare by small valve-like incision through the skin; vein then opened by carefully planned longitudinal incision, into which portions of vegetation from the valve of the heart were at once inserted. More of the same material was introduced under the skin into the wound. The wound was then closed; very slight hemorrhage occurred beneath the skin, where it had been detached, and formed with the material introduced into the wound a hard clot.

EXPERIMENT 3.—Small pocket made in skin of brown rabbit's ear, and a portion of vegetation from aortic valve of heart introduced below the skin.

RESULT.—The three animals remained entirely unaffected, and continued perfectly well for several weeks, during which period they were kept under observation. In the animal employed in Experiment 2 the clot formed at the time of the experiment was subsequently absorbed, and the vein operated on remained patent—a slight scar at the site of the wound was the only evidence of its having been made.

CONCLUSIONS.—The experiments of this series were intended to supplement those of Series 1. In this case an organism present in the disease was with certainty, in all three experiments, introduced under varied conditions into an animal. The organisms had been demonstrated during life in the blood in the one case, and *post mortem* in the vegetation in both cases. The conditions were varied in each of the three experiments. In Experiment 1 a considerable amount (twelve minims) of blood containing an organism was introduced into the circulation of the animal, and lest the foreign particles should be at once devitalized by the healthy blood of the animal, a local focus for morbid action was provided by introducing some of the morbid blood into the subcutaneous tissues of the neck. In Experiment 2 the organisms demonstrated in the vegetation were given access both to the blood stream and to the surrounding tissues, the latter in this case depressed by the operation performed. In Experiment 3 a condition was established similar to that induced in the secondary part of the preceding experiment.

In all three the results are negative, not, however, definitely so as regards the pathogenic power of the organism employed, nor as regards the susceptibility of the animal acted upon. The legal difficulty already referred to here presented itself, in the small number of species at command for experimental purposes. One further measure commended itself for trial even in these unsatisfactory conditions, viz., the employment of very large doses of the morbid material. This was carried out in the last series of experiments.

Third Series (June, 1885).

Inoculation experiments only were here performed, the morbid matter introduced being obtained from a well-marked case of ulcerative endocarditis (A. Blythe), in which the organisms were abundantly present in the vegetation. In this case the *post-mortem* examination was made twenty-four hours after death, the body showed no evidence of putrefaction. A mass of the vegetation was removed with aseptic precautions, mixed with ʒj of distilled water, and rubbed down into an emulsion. A rabbit (brown) was placed under the influence of ether, and its left jugular vein laid bare by an incision two inches long. The needle of a hypodermatic syringe was pushed through the wall of the vein into its lumen, and twenty minims of the emulsion of vegetation injected into the blood stream. The needle was then withdrawn and some of the emulsion deposited in the wound, along with flaky portions of the vegetation; the wound was closed by drawing the parts together, but no sutures were employed. The day after the operation the wound was covered by a dry scab. The animal showed then and subsequently no symptom of ill health.

GENERAL CONCLUSIONS.—No definite result has been attained by these three series of experiments. Some opinions may be based upon them, of which the most important is, that the "much-experimented-on-rabbit" is not susceptible to human ulcerative endocarditis. Had positive results accrued to the methods employed in Series 2 and 3, the method of Series 1 would have been subsequently introduced, in order that by cultivation experiments a distinct *materies morbi* might be separated. The method of Series 1, which may be termed the *mediate* method of investigation, can only in the mean time give results of special interest to the germiculturist, until the *immediate* method of investigation, by direct inoculation of morbid products, has demonstrated some species of animal in which the disease may be experimentally produced.

NOTE BY MR. HARE.—Since the above described experiments were performed, some important experimental work upon the subject has been published, to which it will be well to refer shortly. During last year, Wyssokovitsch,[1] working in the laboratory of Professor Orth, undertook an experimental research with a view to producing ulcerative endocarditis artificially in the lower animals. He made use of rabbits in carrying out these experiments, employing pure cultivations of the micrococci obtained from pus in acute inflammatory conditions as a *materies morbi.* A fine probe was introduced into the carotid artery and passed down to the commencement of the aorta, so as to cause abrasion of the aortic valves. When the valves had been in this way prepared for the supervention of morbid processes, a considerable quantity of the infective material was thrown into the blood stream, and the animal soon exhibited all the symptoms of ulcerative endocarditis, and upon post-mortem examination presented the typical appearances of that disease. By simple injection, without injury of the valves, Wyssokovitsch failed to produce the disease. It was found that when produced artificially, the disease was in the first place strictly limited to the irritated area, spreading not by extension of superficial ulceration but by a destructive process which disintegrated the subjacent tissues. Shortly after the publication of these results the question was taken up by Professor Ribbert, of Bonn, who has now published the results of further experiments.[1] Making use of the *staphylococcus aureus*[2] in pure cultivations, he injected very large quantities of the infective material into the blood stream of rabbits, without in any way causing previous injury of the cardiac valves. By this means he produces an infective myocarditis in all cases; and in cases where very large doses of the infective material are employed, endocarditis is present in addition to the numerous points of suppurative action found in the muscular structure. Vegetations are produced on both sides of the heart, the mitral valve being usually more affected than the tricuspid, whilst the aortic and pulmonary valves are unaffected. If small doses of the infective material be introduced, the animal still dies of a pyæmic condition, but the disease is not so rapidly fatal as in the ulcerative cases. Where ulcerative endocarditis is present, death usually takes place in from twenty to twenty-four hours; where it is not present, the animal may not succumb till the fifth day.

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[1] Centralblatt f. d. med. Wissenschaften, 1885, No. 33.

It comes to be a question how far this experimental pyæmia really coincides with ulcerative endocarditis in the human subject. In their most violent forms the two conditions would appear to be very closely related—*i. e.*, where miliary abscesses and valvular lesions are both present.

Whether the experimental infection corresponds to the less rapid cases of ulcerative endocarditis in the human subject in which pyæmic conditions are absent, must be determined by future investigation. It would appear that there is a close parallelism in certain cases between the action of the pus-producing organism when thrown into the circulation, and that of the special (and, as yet, not fully described) organism associated with ulcerative endocarditis; but this parallelism has not as yet been shown to extend over a sufficiently wide series of cases to establish their identity.

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[1] Fortschritte d. Medicin, Jan. 1886.

[2] Rosenbach, microörganismen bei den Wund-infections-krankheiten des Menschen, 1884.